Caffeine Self-administration, Withdrawal, and Adverse Effects Among Coffee Drinkers

John R. Hughes, MD; Stephen T. Higgins, PhD; Warren K. Bickel, PhD; William K. Hunt, PhD; James W. Fenwick, PhD; Suzy B. Gulliver, PhD; Gina C. Mireault

• **Twenty-two coffee drinkers (three to seven cups per day) underwent repeated double-blind trials to test for caffeine self-administration, withdrawal, and adverse effects. Each trial consisted first of a randomized crossover period of 1 day of decaffeinated coffee and 1 day of caffeinated coffee (100 mg) to assess withdrawal and adverse effects of caffeine. Next, subjects were given 2 days of concurrent access to the two coffees. The relative use of the two coffees was used to assess caffeine self-administration. Reliable caffeine self-administration occurred in three of 10 subjects in study 1 and seven of 12 subjects in study 2. Withdrawal symptoms were headaches, drowsiness, and fatigue. The major adverse effect from self-administration was tremulousness. The occurrence of headaches on substitution of decaffeinated coffee prospectively predicted subsequent self-administration of caffeine. These results indicate that some coffee drinkers exhibit signs of a caffeine dependence, ie, they self-administer coffee for the effects of caffeine, have withdrawal symptoms on cessation, and experience adverse effects.**

(Arch Gen Psychiatry. **1991;48:611-617)**

Caffeine is the most widely used psychoactive drug in the world. For example, 89% of North American adults use either coffee or tea daily.[1] Whether some individuals develop a dependence on caffeine is widely debated.[1-4] Three of the more common criteria for dependence are (1) the substance is being used for pharmacologic effects (ie, its use is a form of drug self-administration), (2) a withdrawal syndrome occurs on cessation of the substance, and (3) substance use is harmful.[5-7]

Caffeine self-administration has not been consistently demonstrated in nonhumans.[4] In humans, early studies suggested that caffeine content influences coffee consumption.[8-10] Three more recent and better-designed studies tested caffeine self-administration with the use of choice paradigms. In these studies, subjects first sampled caffeinated and decaffeinated coffees[11] or capsules[12,13] in a double-blind manner and then made choices of which coffee or capsule to use. In each study, several subjects repeatedly chose the coffee or capsule containing caffeine across several tests.

Caffeine withdrawal in nonhumans decreases locomotor activity,[3] but whether caffeine withdrawal affects physiologic, hormonal, biochemical, or other behavioral processes in nonhumans has not been systematically tested. In humans, abstinence from caffeine produces headache, fatigue, drowsiness, and decreased performance.[3,14] These symptoms occur during blind substitution of decaffeinated coffee and are reversed by administration of caffeine alone.[11,15-17] Whether such withdrawal is important for caffeine self-administration is unclear.[11,18]

Adverse effects of caffeine have been well documented.[14] Symptoms of caffeine intoxication in *DSM-III-R* are restlessness, nervousness, excitement, insomnia, flushed face, diuresis, gastrointestinal tract disturbance, muscle twitching, rambling flow of thought or speech, tachycardia or cardiac arrhythmia, periods of inexhaustibility, and psychomotor agitation. These symptoms can mimic or aggravate psychiatric[19-21] and medical[22] conditions. Whether these symptoms limit caffeine self-administration has not been tested.

The present two studies were done to examine more clearly and systematically caffeine self-administration, withdrawal, and adverse effects among coffee drinkers. We believed this was necessary because the results of previous studies are limited by their sample characteristics (eg, heavy coffee drinkers or those with present or past psychiatric or drug abuse disorders), designs (eg, lack of evidence of within-subject reliability of withdrawal or adverse effects), and measures (eg, use of single choices to infer caffeine self-administration).

SUBJECTS AND METHODS

The methods of studies 1 and 2 were identical except for the packets used to deliver the coffees, as explained below. For brevity, some detailed descriptions of the methods and results have been omitted. These are available from us on request.

Accepted for publication September 10, 1990.

From the Human Behavioral Pharmacology Laboratory, Departments of Psychiatry (Drs Hughes, Higgins, and Bickel), Psychology (Drs Hunt and Gulliver and Ms Mireault), and Medical Biostatics (Dr Fenwick), University of Vermont, Burlington.

Presented in part at the annual meeting of the American Psychiatric Association, Montreal, Quebec, May 6, 1988, and in part at the annual meeting of the Behavioral Pharmacology Society, Annapolis, Md, May 16, 1989.

Reprint requests to Human Behavioral Pharmacology Laboratory, Department of Psychiatry, University of Vermont, 38 Fletcher, Burlington, VT 05401 (Dr Hughes).

Subjects

Eleven subjects in study 1 and 14 in study 2 were recruited via newspaper advertisements. Inclusion criteria were (1) self-reported drinking of three to seven cups of caffeinated coffee per day, (2) reported use of coffee for the effects of caffeine, (3) no use of decaffeinated coffee, (4) use of less than 100 mg/d of caffeine from noncoffee sources, (5) no history of alcohol or drug abuse and use of one or less alcoholic drink per weekday, (6) not trying to stop or reduce caffeine, alcohol, or tobacco use and not on a diet, (7) no present use of prescription or over-the-counter psychoactive medications, (8) no significant psychiatric or medical problem, (9) no medical contraindication to coffee use,[22] and (10) not pregnant, planning to become pregnant, or breast-feeding.

One subject in study 1 and one in study 2 did not complete at least 1 week of testing due to schedule conflicts. Another subject in study 2 was dropped during the 1st week due to sporadic illicit drug use. The remaining 22 subjects were mostly women (20 of 22) and ranged from 19 to 61 years old (Table 1). The mean cups of coffee per day, 5.9 and 4.8 for studies 1 and 2, are at the 78th and 73rd percentiles of coffee use among US adult coffee drinkers (calculated from Table 4 of Schreiber et al[23]).

Table 1.—Subject Characteristics

Subject/Age, y/Sex	Coffee, Cups/d*	Smoker
Study 1		
1/19/M	5.0	No
2/48/F	3.5	No
3/57/F	3.5	No
4/36/F	6.0	No
5/61/F	7.0	No
6/50/F	5.5	No
7/37/F	8.5	No
8/25/F	7.0	Yes
9/47/F	5.0	No
10/35/F	7.0	Yes
Mean†/41.5 ± 13.5/9 F, 1 M	5.9 ± 1.6	8 No, 2 yes
Study 2		
11/44/M	5.5	No
12/30/F	7.0	Yes
13/38/F	3.0	No
14/26/F	3.5	Yes
15/28/F	8.5	Yes
16/51/F	4.0	No
17/22/F	2.5	No
18/38/F	2.5	No
19/45/F	6.0	Yes
20/35/F	3.5	Yes
21/57/F	5.5	No
22/28/F	6.0	No
Mean†/37 ± 10/11 F, 1 M	4.8 ± 1.9	7 No, 5 yes

*Based on 2 days of self-monitoring before study.
†Mean ± SD or total.

Coffees

The coffees used in the experiment were 2 g of instant decaffeinated coffee (Sanka) alone (3 mg of caffeine) or 2 g of instant decaffeinated coffee (Sanka) plus 100 mg of anhydrous caffeine. Lactose (50 mg) was added to each coffee to mask the bitter taste and so that a white powder would appear in each coffee.

We tested the blindness of our coffees by the standard triangle test.[24] Subjects could not discriminate coffees by taste. However, in study 1, six of the 10 subjects identified the coffees on the basis of visual inspection of the packets. Although not statistically significant, this rate of identification (0.60) appeared to be greater than the 0.33 rate expected by chance. Thus, we switched to completely opaque packets in study 2.

Study Design

Each subject underwent six weekly outpatient trials. Each trial consisted of two tests: a 2-day test of withdrawal and adverse effects (Monday and Tuesday) and then a 2-day test for caffeine self-administration (Wednesday and Thursday).

The withdrawal and adverse effects test was a randomized, double-blind, crossover comparing 1 day of ad libitum use of coffee A (Monday) and 1 day of ad libitum use of coffee B (Tuesday). Coffees A and B were the decaffeinated and caffeinated coffees described above. The order of coffees was randomized across subjects and within subjects across trials. At the end of each day, subjects completed a symptom checklist and some behavioral tasks. "Withdrawal" effects were inferred if a behavioral symptom was rated higher or if performance on a behavioral task was worse on the decaffeinated coffee days than on the caffeinated coffee days. "Adverse" effects were inferred if a symptom was rated higher or performance worse on the caffeinated coffee days than on the decaffeinated coffee days. The withdrawal/adverse effects test also served to familiarize subjects with the two coffees before the self-administration test.

The self-administration test consisted of giving subjects 2 days (Wednesday and Thursday) of concurrent access to the same two coffees (A and B) they had just received in the exposure period, again in a double-blind manner. Subjects were instructed to self-administer these two coffees ad libitum. Self-administration of caffeine was inferred if the rate of self-administration of the caffeinated coffee was greater than that of decaffeinated coffees.

Between the trials (Friday, Saturday, and Sunday), subjects used their own coffees.

Initial Meeting

Subjects first read and signed a form stating the study was "to test whether coffees of different strengths or with different caffeine contents affect your liking of that coffee, how you feel, your behavior, and your performance." Subjects then completed a questionnaire on their demographics and coffee and caffeine intake and completed a brief psychomotor computer task, the Digit Symbol Substitution Task.[25] In study 2, subjects also completed a tremor task.[26]

Withdrawal and Adverse Effects Test

Subjects returned on a Sunday evening to hand in their self-monitoring cards and to pick up coffee A for Monday. They were given three cups with 8-oz marks to use with the coffees. Subjects were instructed as follows: (1) Tomorrow do not use any coffee (decaffeinated or caffeinated) other than what we give you. (2) Do not use any other forms of caffeine (eg, tea or cola). (3) Use the coffee ad libitum with the cup we have provided. (4) Record the time you begin each coffee on the label on the packet. (5) Drink the entire cup within 15 minutes. (6) Drink at least four cups of coffee a day. (7) Do not change the amount of sugar or cream in the coffee across cups or days. (8) Do not change your activity level, diet, or rate of smoking. (9) Abstain from alcohol during the day. (10) Return all used and unused packets of coffee at the next session.

Subjects came back on Monday night, returned their coffees, and completed the computer and tremor tasks as in the introductory session. They also completed a 27-item symptom checklist in which putative symptoms of caffeine withdrawal and adverse effects were listed together in alphabetical order. In study 2, subjects completed the Profile of Mood States,[27] a standardized questionnaire sensitive to caffeine effects.[28] Subjects picked up

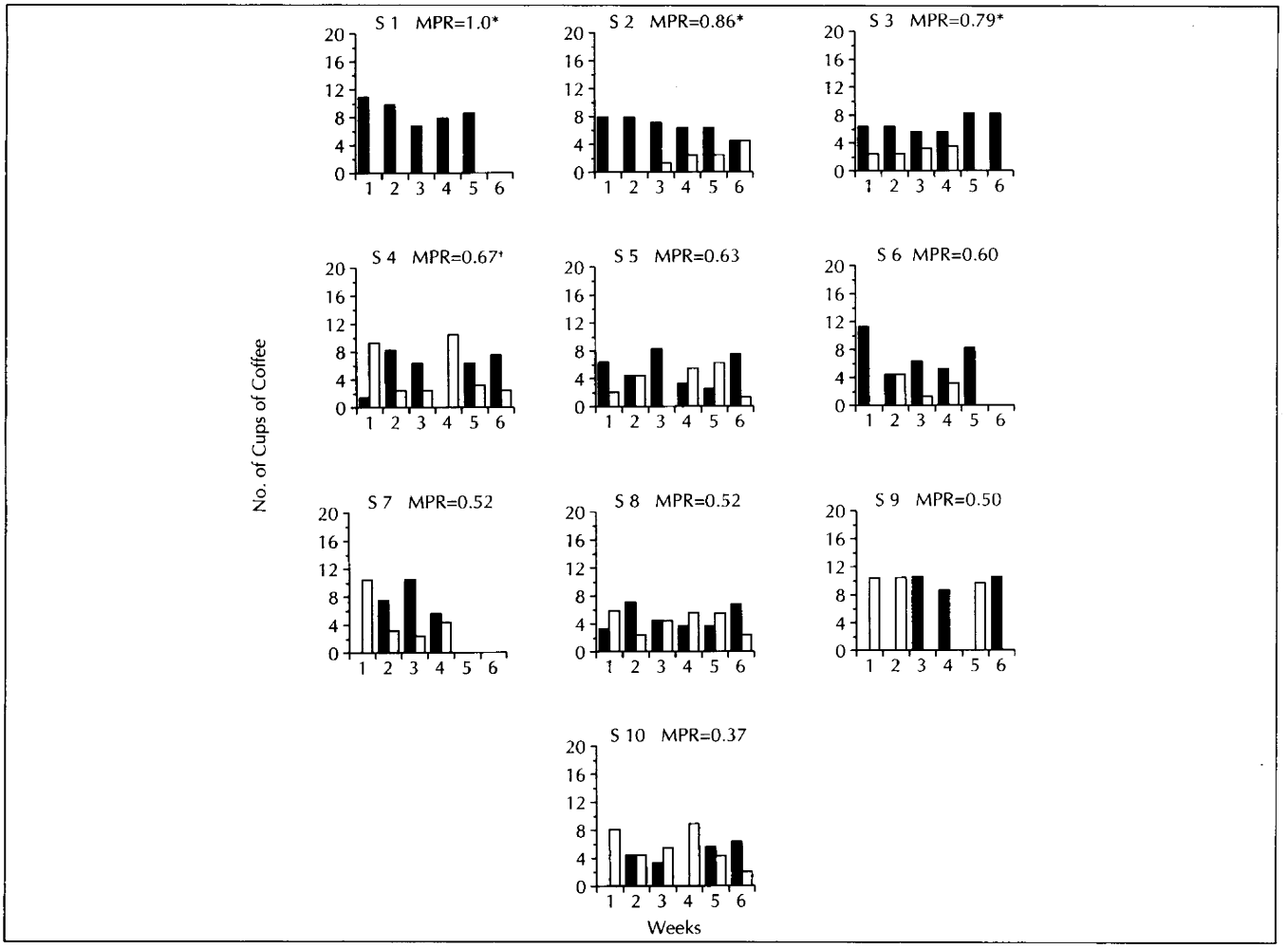

Fig 1.—*Number of cups of coffee self-administered during 2-day tests for study 1. MPR indicates mean preference ratio across trials; S, subject; closed bars, caffeinated coffee; open bars, decaffeinated coffee; asterisk, P<.001; and dagger, P<.05.*

coffee B to use on Tuesday with the same instructions as for Monday. Coffee B was the converse of coffee A.

Subjects returned on Tuesday evening, returned their coffees, and completed the self-report, computer, and tremor tasks as before.

Self-administration Test

On Tuesday evening, subjects were given both coffees A and B to use on Wednesday and Thursday. Subjects were given the following additional instructions: (11) Coffees A and B are the same as those you received on Monday and Tuesday. (12) Use either coffee A or B as you wish. You may use one coffee exclusively or you may switch back and forth as often as you like. (13) You must wait 60 minutes when you switch from one coffee to another.

Subjects were required to drink four cups of coffee per day as in the withdrawal and adverse effects test. They returned on Thursday evening to turn in their coffees.

Data Analysis

Analyses were first conducted to determine if caffeine self-administration, withdrawal, or adverse effects occurred within a given subject and then whether the effects occurred across all subjects. In the within-subject analyses, both a repeatability criterion (ie, consistency across trials) and a statistical criterion (ie, tests of proportion or Mantel-Haenszel tests) were used to infer positive results. Analyses were done separately for studies 1 and 2 to assess for replication across studies.

RESULTS

The results of studies 1 and 2 were similar and are presented concurrently. Among the 22 subjects who completed at least 1 week, two (subjects 1 and 6) dropped out in the last week of study 1, one (subject 7) in the next-to-last week of study 1, and one (subject 22) in the 2nd week of study 2.

Self-administration

In study 1, several subjects consistently chose caffeinated coffee in preference to decaffeinated coffee (Fig 1). The repeatability criterion was set at greater self-administration of caffeinated coffee than decaffeinated coffee on at least five of the six self-administration tests. In study 1, three of the 10 subjects (subjects 1 through 3) met this criterion (subject 7 self-administered caffeine on three of four occasions but then dropped out). In study 2, to save effort, any subject who did not self-administer more caffeinated coffee than decaffeinated coffee on two trials was dropped, as that subject could not pass our repeatability criterion. In study 2, seven (subjects 11 through 17) of the 12 subjects self-administered more caffeinated coffee than decaffeinated coffee on at least five of the six trials (subject 22 self-administered caffeine on one occasion but then dropped out) (Fig 2).

For the within-subjects statistical criterion, preference ratios (PRs)[29] were calculated for each self-administration test as the proportion of coffee self-administrations that were of caffeinated coffee. Thus, a PR of 0.5 would indicate equal self-administration of decaffeinated and caffeinated coffees, and a PR of 1.0 would indicate exclusive self-administration of caffeinated

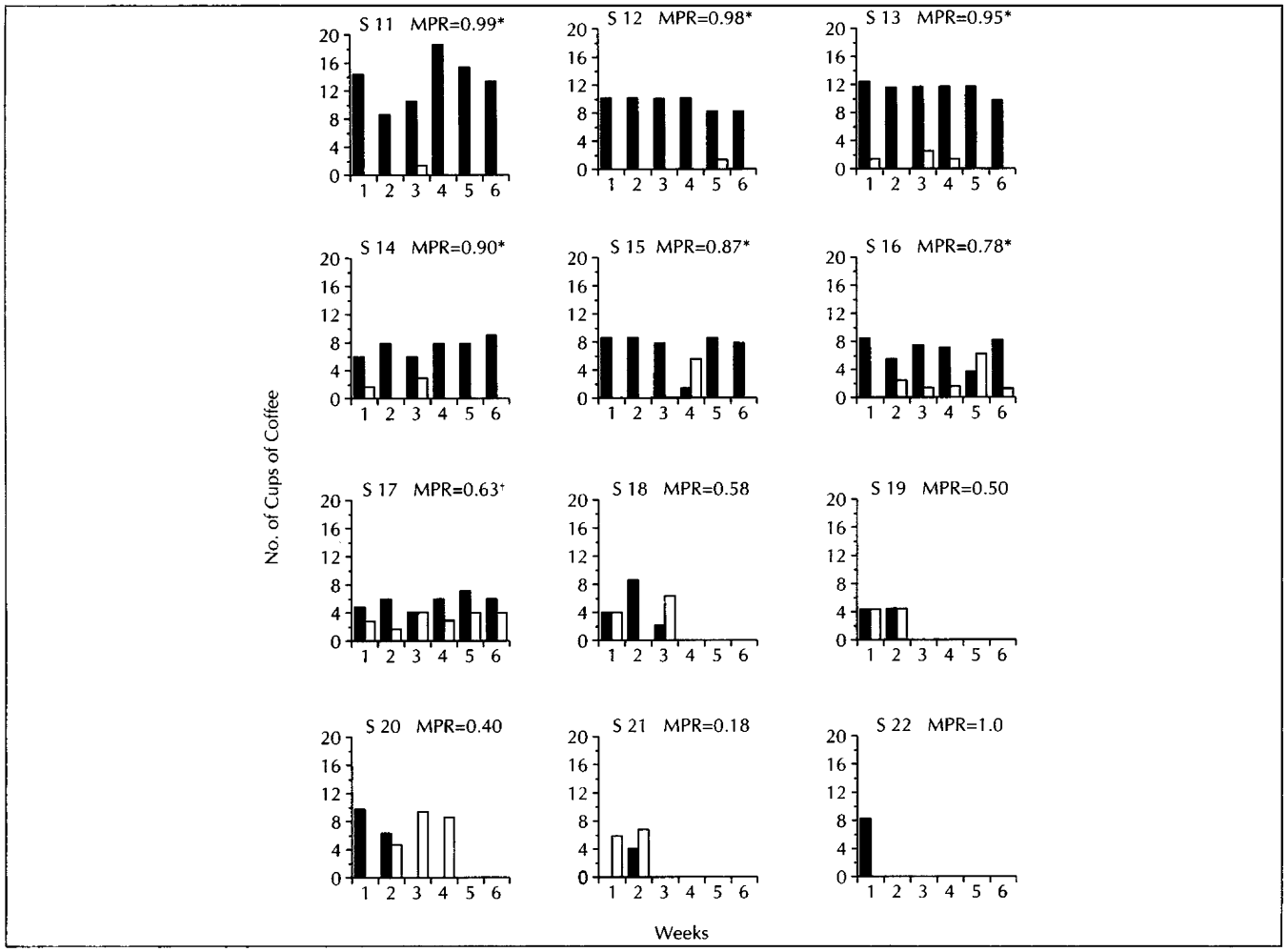

Fig 2.—*Number of cups of coffee self-administered during 2-day tests for study 2. MPR indicates mean preference ratio across trials; S, subject; closed bars, caffeinated coffee; open bars, decaffeinated coffee; asterisk, P<.001; and dagger, P<.05.*

coffees. Next, a mean PR (MPR) for each subject was calculated by averaging the PRs across all trials.

All of the subjects in studies 1 and 2 who passed the repeatability criterion also had an MPR that was significantly greater than the expected MPR of 0.5 (MPRs >0.63, $P<.001$, test of proportions (Fig 1). In addition, among those who did not meet the repeatability criterion in study 1, one subject (subject 4) had an MPR significantly greater than 0.5 (0.67; $P=.01$) and one (subject 5) had an MPR nonsignificantly greater than 0.5 (0.63; $P=.07$).

Self-monitored times of coffee self-administration during the withdrawal and adverse effects test showed a bimodal distribution, with 50% of the coffees self-administered between 6 AM and 10 AM. Caffeinated coffee was not self-administered earlier in the day than decaffeinated coffee.

In study 1, after each exposure period but before the subsequent test period, subjects reported which coffee they would choose if forced to choose. This self-report was concordant with subsequent choice behavior in the test period of 41 trials and discordant on 14 trials.

The probability of caffeine self-administration (and of withdrawal effects and adverse effects) was similar whether the 1st or 2nd day of the withdrawal and adverse effects period was a day of decaffeinated coffee only or a day of caffeinated coffee only.

Caffeine Withdrawal

For within-subject analyses of withdrawal, the repeatability criterion described above (five of six tests) was used again. The statistical criterion was a Mantel-Haenszel test, as the data were ordinal and highly skewed (many zero scores) in a relatively small sample.

Three subjects in study 1 (subjects 2, 3, and 5) and four in study 2 (subjects 11, 13, 14, and 17) reliably reported headaches, drowsiness, and/or fatigue according to both the repeatability and statistical criterion (Table 2). One additional subject (subject 4) in study 1 and one (subject 12) in study 2 reliably reported withdrawal effects by one criterion but not the other.

Across subjects, drowsiness, fatigue, and headaches were reported significantly more on decaffeinated coffee days than on caffeinated coffee days in both studies 1 and 2 ($\chi^2>4.2$, $P<.05$).

Anxiety, irritability, impatience, mood swings, nausea, and restlessness were not significantly greater on decaffeinated days in either study. Similarly, in study 2, in which the Profile of Mood States was administered, subjects reported lower scores on the vigor and higher scores on the fatigue scales ($\chi^2>5.0$, $P<.025$) but not higher scores on the anger or confusion scales with decaffeinated than caffeinated coffee.

Drowsiness, fatigue, and headaches occurred (ie, were greater with decaffeinated coffee than with caffeinated coffee) in 38% to 41% of trials in study 1 and 32% to 39% in study 2. These symptoms were rated as severe on a significant minority of trials, ie, 11% to 16% in study 1 and 6% to 19% in study 2.

On the psychomotor task, subjects made more errors with decaffeinated coffee than caffeinated coffee (mean, 4.8±4.0 vs 2.5±2.1; $F=3.8$, $P=.05$). The number of trials attempted and response rate did not differ between coffees.

Table 2.—Comparison of Self-administration, Withdrawal, and Adverse Effects Across Subjects*

Subject	Self-Administered Caffeine	Caffeine Withdrawal	Adverse Effects
	Study 1		
1	+ +	−	+
2	+ +	+ +	+ +
3	+ +	+ +	−
4	+	+	+
5	?	+ +	+
6	−	−	−
7	−	−	+
8	−	−	−
9	−	−	−
10	−	−	−
	Study 2		
11	+ +	+ +	−
12	+ +	+	−
13	+ +	+ +	−
14	+ +	+ +	−
15	+ +	−	−
16	+ +	−	−
17	+ +	+ +	+
18	−	−	−
19	−	−	−
20	−	−	−
21	−	−	−
22	−	−	−

*Two plus signs indicate passed both repeatability and within-subjects statistical criteria ($P<.05$); one plus sign, passed only within-subjects statistical criteria ($P<.05$); question mark, nonsignificant trend to pass within-subjects statistical criteria ($P<.10$); and minus sign, did not pass either repeatability or within-subjects statistical criteria ($P<.05$).

Adverse Effects of Caffeine

During the withdrawal and adverse effects testing, subjects self-administered an average of 456 mg/d of caffeine in study 1 and 431 mg in study 2. Only one subject (subject 2) consistently reported an adverse effect of caffeine (ie, tremulousness consistently greater on caffeinated coffee days than on decaffeinated coffee days) across both the repeatability and within-subject statistical criteria (Table 2). Four subjects in study 1 (subjects 1, 4, 5, and 7) and one in study 2 (subject 17) reliably reported an adverse effect by one of the criteria.

Across subjects, tremulousness was reported significantly more often on caffeinated coffee than on decaffeinated coffee days in both studies 1 and 2 ($P<.05$). Anxiety, frequent urination, muscle twitches, nausea, restlessness, stomachache, sweating, talkativeness, and tinnitus were significantly greater on caffeinated coffee days in one study and showed a similar nonsignificant trend in the other study. Palpitations were of borderline significance ($P<.10$) in both studies. Depression, diarrhea, dizziness, impatience, irritability, and mood swings were not significant in either study. On the Profile of Mood States taken in study 2, subjects reported more anxiety ($\chi^2=6.0$, $P=.02$) but not more depression with caffeinated than decaffeinated coffee. On the tremor test in study 2, the number of contacts did not differ between the coffees.

In both studies, adverse symptoms were of small magnitude and prevalence (ie, <30%) and only rarely (<10%) were rated as severe.

Prediction of Caffeine Self-administration, Withdrawal, and Adverse Effects

Almost all of the subjects who reliably reported withdrawal effects (subjects 2 through 5, 11 through 13, and 17) were subjects who reliably self-administered caffeine (Table 2). Across all tests, the occurrence of headache prospectively predicted subsequent caffeine self-administration in study 2 ($\chi^2=4.4$, $P<.03$). A similar nonsignificant trend occurred in study 1. None of the other withdrawal symptoms prospectively predicted self-administration. Adverse effects did not predict lesser or greater self-administration of caffeine.

Across both studies, the usual number of cups per day, usual milligrams of caffeine per day, duration of coffee use, and number of attempts to stop drinking coffee did not predict caffeine self-administration, withdrawal, or adverse effects. Subjects who drank more cups per day and consumed more caffeine (milligrams per day) had marginally greater adverse effects ($r=.30$, $P=.09$ for both).

Caffeine self-administration was similar between smokers (three of 17) and nonsmokers (seven of 15) and occurred in many of the women (eight of 20) and both of the men.

COMMENT

Caffeine Self-administration

The major finding of this study was that reliable caffeine self-administration occurred in three coffee drinkers in study 1 and seven coffee drinkers in study 2. Since these subjects were tested repeatedly with independent tests and passed both repeatability and statistical criteria, there is little doubt that these 10 subjects self-administered our coffees for the effects of caffeine.

This study differed from previous studies of caffeine self-administration in three ways. First, the present study used a multiple-choice concurrent-access procedure. We believe that this procedure provided a more rigorous test of caffeine self-administration than previous studies did because, in contrast to self-administration studies in which only one coffee was available,[8-11] our concurrent-access procedure required subjects to self-administer caffeinated coffees in the presence of readily available decaffeinated coffee. In addition, in contrast to single-choice studies,[11-13] our concurrent-access procedure required subjects to choose repeatedly between self-administering caffeinated or decaffeinated coffees during a 48-hour period, ie, caffeine had to control behavior across a number of choice tests rather than a single choice test.

A second difference in our study was its ability to demonstrate reliable caffeine self-administration within a given subject. In most previous studies, caffeine self-administration was tested either only once[9,10] or two to three times[8,11,13] within an individual. The one exception was a study that reported that caffeine self-administration occurred on at least eight of 10 choice tests in five subjects.[12]

A third difference between this study and previous studies is the sample. Early studies of caffeine self-administration used special populations, eg, very heavy coffee drinkers with histories of drug abuse.[8,11] The one exception was a study that used subjects with a wide range of caffeine intakes.[12] The positive results of this previous study plus our own suggest that special histories, such as heavy coffee use or drug abuse, are not necessary for caffeine self-administration.

Although we have argued that our procedure is rigorous, it differs in two respects from traditional procedures to establish drug self-administration in nonhumans. First,

we instructed subjects to self-administer at least four cups of coffee per day during the 2-day test periods. This was done to ensure a number of choices between caffeinated and decaffeinated coffees. We have completed a follow-up study in which caffeine self-administration occurred even when subjects were not instructed to consume a certain number of cups per day.[30]

Second, nonhuman studies of drug self-administration usually require some behavior to produce drug self-administration (eg, a certain number of lever presses). In the present study, the response effort to self-administer the coffees was minimal. Whether caffeine self-administration would occur in the face of significant response costs will require further study. However, in a study in our laboratory, some coffee drinkers repeatedly made 1000 to 2500 lever pulls to obtain a 2-oz serving of caffeinated coffee (W.K.B., J.R.H., S.T.H., and R. J. DeGrandpre, MS, and P. Rizzuto, unpublished data, 1990).

Thus far, we have emphasized the positive results of the study, ie, that reliable caffeine self-administration occurred in 10 coffee drinkers. However, two other points require comment. First, the other 11 coffee drinkers stated that they drank coffee for the effects of caffeine yet did not show reliable caffeine self-administration. Perhaps when such factors as caffeine dose, fatigue, and performance demands are manipulated, caffeine self-administration would occur in these subjects. Second, our subjects had histories of self-administering only caffeinated coffee, yet several of them self-administered significant amounts of decaffeinated coffee in the study (eg, subjects 4 and 9). This result may have occurred because the nonpharmacologic sensory characteristics of coffee (eg, taste) are inherently reinforcing or because these sensory cues have become conditioned reinforcers by a long history of being reliably paired with the pharmacologic effects of caffeine.

Caffeine Withdrawal

Headaches, drowsiness, and fatigue were reported more frequently on decaffeinated coffee days than on caffeinated coffee days during the withdrawal and adverse effects period. We have labeled these "withdrawal" effects due to substitution of decaffeinated coffee. Caffeine has a half-life of 2 to 6 hours.[1-3] At the time subjects completed forms on the decaffeinated coffee days, most subjects had been deprived of caffeine for 24 to 30 hours (or 4 to 12 half-lives); thus, it is reasonable to expect withdrawal effects to have occurred.

On the other hand, demonstration of withdrawal effects usually requires evidence that the effects are time limited, differ from those seen in non–drug users, etc.[31] The present study lacks such evidence; however, several other studies have provided such evidence for headache, drowsiness, and fatigue as symptoms of caffeine withdrawal.[3]

Previous studies of caffeine withdrawal have not systematically evaluated the magnitude or replicability of withdrawal symptoms. Our results indicate that, in some individuals, headache, drowsiness, and fatigue are very reliable and sometimes severe withdrawal symptoms.

Withdrawal and Caffeine Self-administration

In the present study, the occurrence of headaches on substitution of decaffeinated coffee prospectively predicted subsequent caffeine self-administration. Drug withdrawal has been posited to be a factor in human drug self-administration across several drugs; however, the experimental database for such a conclusion is surprisingly scant.[32] More recent work has focused on the positive reinforcing of drugs.[6]

Previous data on the relationship of withdrawal and caffeine self-administration have been contradictory. In one study, caffeine self-administration occurred when caffeine intake had been recently terminated (and subjects presumably were in withdrawal) but not when caffeine had been stopped for 10 days (and subjects were presumably no longer in withdrawal).[11] A second study of experimentally induced physical dependence on caffeine in humans failed to replicate this finding.[18]

The association of headaches and caffeine self-administration in the present study should not be overinterpreted. For example, headaches do not appear to be a necessary condition for caffeine self-administration, as three subjects reliably self-administered caffeine but did not reliably report headaches on substitution of decaffeinated coffee (subjects 1, 15, and 16).

Adverse Effects of Caffeine

In the present study, several subjects who consumed 400 to 500 mg of caffeine during the withdrawal and adverse effects period reliably reported stomachache, sweating, talkativeness, tinnitus, and tremulousness. Thus, consistent with previous reviews,[14] our data suggest that adverse effects can occur at intakes equivalent to four 6-oz cups of brewed coffee per day.

CONCLUSION

Our results indicate that some coffee drinkers exhibit common signs of a drug dependence,[5-7] ie, they self-administer coffee for the effects of caffeine, have withdrawal symptoms on cessation of caffeine, and experience adverse effects from caffeine intake. On the other hand, neither the present study nor previous studies have demonstrated that coffee drinkers fulfill other *DSM-III-R* criteria for psychoactive substance dependence, eg, unsuccessful efforts to cut down or control caffeine use, use of caffeine despite knowledge of having a problem caused by the caffeine, or tolerance to the behavioral effects of caffeine.

Whether caffeine use can be a form of a drug dependence will be a controversial topic. Hopefully, empiric data as in the present and previous studies[3,4] rather than a priori beliefs will guide decisions on the presence, magnitude, and significance of caffeine dependence.

This study was funded by grant DA 04843, Research Scientist Development Award DA 00109 (Dr Hughes), and First Independent Research Scientist Award DA 04545 (Dr Higgins) from the National Institute on Drug Abuse, Bethesda, Md.

We thank Sara Pepper for help in running the study and Neil Benowitz, Warren Bickel, and Steve Holtzman for their comments on the manuscript.

References

1. Gilbert RM. Caffeine as a drug of abuse. In: Gibbons RJ, Israel Y, Kalant H, Popham RE, Schmidt W, Smart RG, eds. *Research Advances in Alcohol and Drug Problems*. New York, NY: John Wiley & Sons Inc; 1976;3:49-176.

2. Gilliland K, Bullock W. Caffeine: a potential drug of abuse. In: *The Addictive Behaviors*. New York, NY: Hawthorne Press; 1984:53-73.

3. Griffiths RR, Woodson PP. Caffeine physical dependence:

a review of human and laboratory animal studies. *Psychopharmacology.* 1988;94:437-451.

4. Griffiths RR, Woodson PP. Reinforcing properties of caffeine: studies in humans and laboratory animals. *Pharmacol Biochem Behav.* 1988;29:419-427.

5. American Psychiatric Association, Committee on Nomenclature and Statistics. *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition.* Washington, DC: American Psychiatric Association; 1987.

6. Jaffe JH. Drug addiction and drug abuse. In: Gilman AG, Goodman LS, Gilman A, eds. *The Pharmacologic Basis of Therapeutics.* New York, NY: Macmillan Publishing Co Inc; 1980:535-584.

7. Tobacco use as drug dependence. In: Benowitz NL, Grunberg NE, Henningfield JE, Lando HA, eds. *The Health Consequences of Smoking: Nicotine Addiction: A Report of the Surgeon General.* Washington, DC: US Department of Health and Human Services; 1988:145-240. DHHS publication (CDC) 88-8406.

8. Griffiths RR, Bigelow GE, Liebson IA, O'Keefe M, O'Leary D, Russ N. Human coffee drinking: manipulation of concentration and caffeine dose. *J Exp Anal Behav.* 1986;45:133-148.

9. Kozlowski LT. Effect of caffeine on coffee drinking. *Nature.* 1976;264:354-355.

10. Podboy JW, Mallory WA. Caffeine reduction and behavior change in the severely retarded. *Ment Retard.* 1977;15:40.

11. Griffiths RR, Bigelow GE, Liebson IA. Human coffee drinking: reinforcing and physical dependence producing effects of caffeine. *J Pharmacol Exp Ther.* 1986;239:416-425.

12. Griffiths RR, Woodsen PP. Reinforcing effects of caffeine in humans. *J Pharmacol Exp Ther.* 1989;246:1-8.

13. Stern KN, Chait LD, Johanson CE. Reinforcing and subjective effects of caffeine in normal human volunteers. *Psychopharmacology.* 1989;98:81-88.

14. Greden JF. Caffeinism and caffeine withdrawal. In: Lowinson JH, Reiz P, eds. *Substance Abuse: Clinical Problems and Perspectives.* Baltimore, Md: Williams & Wilkins; 1981:274-286.

15. Dreisbach RH, Pfeiffer C. Caffeine-withdrawal headache. *J Lab Clin Med.* 1943;28:1212-1219.

16. Goldstein A, Kaiser S, Whitby O. Psychotropic effects of caffeine in man, IV: quantitative and qualitative differences associated with habituation to coffee. *Clin Pharmacol Ther.* 1969;10:489-497.

17. Goldstein A, Kaiser S. Psychotropic effects of caffeine in man, III: a questionnaire survey of coffee drinking and its effects in a group of housewives. *Clin Pharmacol Ther.* 1969;10:477-488.

18. Evans S, Griffiths R. The effects of chronic caffeine exposure on the reinforcing properties of caffeine. In: Harris LS, ed. *Problems of Drug Dependence, 1988.* Bethesda, Md: National Institute on Drug Abuse. In press. NIDA research monograph 90.

19. Furlong FW. Possible psychiatric significance of excessive coffee consumption. *Can Psychiatr Assoc.* 1975;20:577-583.

20. Greden JF. Anxiety or caffeinism: a diagnostic dilemma. *Am J Psychiatry.* 1974;31:1089-1092.

21. Wells SJ. Caffeine: implications of recent research for clinical practice. *Am J Orthopsychiatry.* 1984;54:375-389.

22. Hughes JR, Amori G, Hatsukami DK, Lavigne F. A survey of physician advice about caffeine. *J Substance Abuse.* 1988;1:67-70.

23. Schreiber GB, Maffeo CE, Robins M, Masters MN, Bond AP. Measurement of coffee and caffeine intake: implications for epidemiologic research. *Prev Med.* 1988;17:280-294.

24. Amerine MAA, Pangborn RM, Roessler EG. *Principles of Sensory Evaluation of Food.* Orlando, Fla: Academic Press Inc; 1965.

25. McLeod DR, Griffiths RR, Bigelow GE, Yingling J. An automated version of the digit symbol substitution test (DSST). *Behav Res Methods Instrumentation.* 1982;14:463-466.

26. Myrsten AL, Elgerot A, Edgren B. Effects of abstinence from tobacco smoking on physiological and psychological arousal levels in habitual smokers. *Psychosom Med.* 1977;39:25-38.

27. McNair DM, Lorr M, Droppelman LF. *Manual for the Profile of Mood States.* San Diego, Calif: Educational and Industrial Testing Service; 1971.

28. Chait LD, Griffiths RR. Effects of caffeine on cigarette smoking and subjective response. *Clin Pharmacol Ther.* 1983;34:612-622.

29. Hughes JR, Pickens RW, Spring W, Keenan R. Instructions control whether nicotine will serve as a reinforcer. *J Pharmacol Exp Ther.* 1985;235:106-112.

30. Oliveto AH, Hughes JR, Pepper SL, Bickel WK, Higgins ST. Low doses of caffeine can serve as reinforcers in humans. In: Harris LS, ed. *Problems of Drug Dependence, 1990.* Bethesda, Md: National Institute on Drug Abuse. In press. NIDA Research Monograph Series.

31. Hughes JR, Higgins ST, Hatsukami DK. Effects of abstinence from tobacco: a critical review. In: Kozlowski LT, Annis H, Cappell HD, Glaser F, Goodstadt M, Israel Y, Kalant H, Sellers EM, Vingilis J, eds. *Research Advances in Alcohol and Drug Problems.* New York, NY: Plenum Press; 1990;10:317-398.

32. Cappell H, LeBlanc AE. Tolerance and physical dependence: do they play a role in alcohol and drug self-administration? In: Yedy I, Glaser FB, Kalant H, Popham R, Schmidt W, Smart RG, eds. *Research Advances in Alcohol and Drug Problems.* New York, NY: Plenum Press; 1981;6:159-196.